Long term oral immunotherapy management and assessment of success

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ABSTRACT

There is limited data addressing the optimal dose, dosing frequency, and duration of OIT maintenance. Using higher maintenance doses, more frequent dosing, and a long dosing duration makes it more likely that sustained unresponsiveness will be achieved but also increases the burden of care on the OIT patient and family. The OIT maintenance regimen should be individualized based on the treatment goals of the patient and family.

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Reaching the oral immunotherapy (OIT) escalation target dose and beginning maintenance dosing is not the goal of OIT, it is merely the end of the beginning. The goal of OIT is not just desensitization but specific improvement in the quality of life of the patient and family. Ideally, all patients would like to achieve the tolerance that is the normal relationship between a person and a food so that eating requires no precautions; however, the degree to which this is possible for an individual patient is unknown.[1–4] The actual OIT goals are more concrete and can be considered benchmarks in a continuum that begins with complete avoidance and culminates with unrestricted consumption of the allergenic food without postconsumption activity restrictions or the need to carry epinephrine. These benchmarks are listed in Table 1. Although all patients and families want to achieve protection against cross-contamination exposures and accidental ingestions, the importance of *ad libitum* incorporation of the OIT food into the diet, less than daily maintenance dosing, and the elimination of postdosing activity restrictions varies among patients. It is crucial for the OIT practitioner to understand what is important to each family as well as the goals that are realistic for the patient.

The design of an OIT maintenance regimen requires the definition of the dose, the dosing frequency, and the duration of maintenance. There is some guidance from published experience[5,6] and extrapolation from experience with subcutaneous immunotherapy to aid the clinician in defining these parameters. Higher doses, more frequent dosing, and more prolonged dosing are thought to increase the likelihood of achieving the goals of dietary incorporation or sustained unresponsiveness (SU). Unfortunately, this simplistic formulation is not very helpful because, having to consume a high dose every day forever is not an attractive plan. The unknowns that complicate defining a maintenance regimen are listed in Table 2.

MAINTENANCE PROTOCOLS, INCLUDING ACTIVITY LIMITATIONS

Maintenance protocols are intended to preserve the desensitization achieved during dose escalation. Maintenance dosing continues formally or informally (see the incorporating the OIT food into the routine diet section) indefinitely or until SU (below) is achieved. As noted above, the most appropriate dose, the dosing frequency, and the duration of dosing are likely to vary from patient to patient but, at this time, the ideal maintenance dose, dosing frequency, and duration of maintenance dosing are unknown. The OIT maintenance dose may depend on the patient's desensitization goal. That is, some patients may choose to be desensitized to a modest goal that protects against most accidental exposures (*e.g.*, 300 mg of peanut protein) and continue to practice elimination of the OIT food from the diet,[7] whereas other patients may desensitize to a higher dose (6000 mg of peanut protein) and incorporate the OIT food into the diet.[8] Commonly used regimens vary from daily dosing for a minimum of 3 years to daily dosing for 6 months, followed by a gradual reduction in dosing frequency to once or twice

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Table 1 **Benchmarks in oral immunotherapy**

1. Protection against cross-contamination exposure
2. Protection against accidental ingestion
3. *Ad libitum* incorporation of the allergenic food into the routine diet
4. Discontinuation of scheduled oral immunotherapy dosing
5. Elimination of activity (exercise) restrictions after exposure
6. No longer needing immediate availability of epinephrine

Table 2 **Unanswered questions about oral immunotherapy**

1. What is the ideal maintenance dose?
2. What is the most effective dosing schedule?
3. What is the duration of dosing necessary to achieve the patient's goal(s)?
4. Are there biomarkers that predict the likelihood of sustained unresponsiveness?
5. How should factors 1, 2, and 3 (listed in this table) vary?
6. Can the dose or dosing frequency be reduced at some point without compromising the patient's ability to reach his or her goal?
7. Are there patient-specific factors that predict the oral therapy outcome and need for a particular maintenance regimen?
8. Are there patients who will never achieve all of the benchmarks listed in Table 1 but who can meet more limited goals with a less burdensome maintenance regimen?

a week. Maintenance doses range from <100 mg of treatment food protein to 2000 mg of nut protein, 4000 mg of wheat protein, 5000 mg of egg protein, and 8000 mg of cow's milk protein.[9]

It has been estimated that the ability to tolerate 300 mg of peanut protein will protect against 95% of accidental ingestions (within the OIT community, this is referred to as "bite-proofing").[10] Data from a study of Palforzia, Aimmune Therapeutics, Brisbane, CA, showed that many patients who are maintained at 300 mg of peanut protein daily are able to tolerate more than four times that dose.[5] The choice of a maintenance dose should be determined by the OIT goals; cross-contamination protection, bite-proofing, or free eating (within the OIT community, free eating means the unrestricted incorporation of full-meal servings of the OIT food, *e.g.*, a peanut butter sandwich). The maintenance dose should be higher for patients who plan to incorporate the food into their diet. Many patients in OIT dislike their OIT food and will avoid it despite OIT. Those patients may use a lower maintenance dose. Lower maintenance doses of peanut OIT have been found to improve dosing persistence.[11] Lower maintenance doses reduce the patient's burden of care; however, the dose that is most likely to lead to SU is unknown.

Some practitioners decrease the maintenance dosing frequency on a schedule determined by changes in specific IgE levels or skin-prick testing results, whereas others periodically challenge their patients to several times the maintenance dose before a dose frequency reduction. Neither of these modifications has been tested in formal studies. At least one study has shown that, reducing the dosing frequency too quickly may jeopardize the desensitization.[5] The ideal regimen that minimizes the burden of care while maximizing OIT efficacy remains to be determined. The ideal regimen for an individual patient should be based on shared decision-making discussions with the patient and family.

INCORPORATING THE OIT FOOD INTO THE ROUTINE DIET

For those patients whose goal is to not to have to avoid their OIT food once desensitization has been achieved, the OIT food may be incorporated routinely into the regular diet in addition to their daily OIT maintenance dose. At the Dallas Food Allergy Center, the escalation target dose is equal to a full-meal serving of the OIT food and then a somewhat lower maintenance dose is used.[8] The quantities of milk, egg, wheat, and, for some patients, peanut butter, chickpeas, beans, and other foods consumed as a single portion may equal or exceed the OIT maintenance dose. Patients and parents should be cautioned that it may be possible to exceed the desensitization and induce a reaction. An example of this kind of problem is the use of protein powder supplements that may contain as much as 24 g of cow's milk protein in a single serving.

Because exercise-induced food allergy reactions are common during OIT, most clinicians insist on a postdosing period of exercise restriction of a least two hours. Some patients require a longer period of restriction. Exercise restrictions become more problematic when the food is routinely incorporated into the diet. Because the necessary postdosing restriction varies among patients, activity limitations after other exposures to the OIT food must be individualized. Most patients in OIT do well with a 2-hour postdosing activity restriction. Many such patients do well with no restriction if the exposure is less than half of the OIT maintenance dose, a 1-hour restriction if the exposure is half of the OIT maintenance dose, and a 2-hour restriction if the exposure is more than half of the OIT maintenance dose (personal observation). One study of peanut OIT reported that the majority of maintenance reactions (many of which were triggered by violation of the 2-hour activity restriction) occurred

Table 3 **Possible predictors of successful sustained unresponsiveness challenge**

Amount of maintenance dose
Duration of maintenance dosing
Time interval since the last reaction to maintenance dosing
Change in food specific IgE level or skin-prick testing results
Basophil activation test

during the first 6 months after reaching maintenance,[8] which implies that the need for postexposure activity limitation may diminish over time. Other reaction risk factors (*e.g.*, menses, nonsteroidal anti-inflammatory drug exposure, infection) are addressed elsewhere in this issue.

SU

The process of OIT desensitizes the patient to the OIT food and that desensitization is maintained by regular exposure to the OIT food. The definition of regular in this context varies among patients but virtually all patients in maintenance OIT are able to tolerate at least a 48- to 72-hour interval between exposures. SU is defined as the ability of a patient in OIT to eat his or her OIT food without a reaction after a prolonged period (weeks to months) of abstinence. The term "sustained unresponsiveness" was coined because the relationship among true food tolerance, the natural ability of a person to eat a food at any time, and the status after OIT is unknown. There are different definitions of the duration of abstinence required to label a patient as having SU but 2 weeks is considered the minimum. Some clinicians use 4 weeks as the interval between the last exposure and SU challenge.

There are no established criteria for performing SU challenge but possible predictors of being able to pass SU challenge are shown in Table 3. An example of criteria used to consider SU challenge is shown in Table 4. At the Dallas Food Allergy Center, 85% of patients who meet the criteria listed above pass full-meal challenge after avoiding their OIT food for 30 days. SU challenge itself is performed according to routine challenge protocols and should end with a full-meal serving. Because there have been reports of patients with food allergy who had outgrown their food allergy by passing challenge and subsequently reacting, some clinicians recommend that patients who pass an SU challenge continue to be exposed to the SU food at least once a week. At the Dallas Food Allergy Center, patients who pass an SU challenge no longer have to carry epinephrine. Many patients who meet

Table 4 **Criteria for performing sustained unresponsiveness challenge at the Dallas Food Allergy Center**

OIT maintenance dosing for at least 3 years
No reactions of any kind to the OIT food for at least 1 year
For patients with a pretreatment sIgE level of >10 kU/mL, a decrease of the sIgE level to <2 kU/mL
For patients with a pretreatment sIgE level of <10 kU/mL, a decrease of the sIgE level to <1 kU/mL
If SPT is used for monitoring, then the SPT result should be significantly lower than the pretreatment SPT result

OIT = Oral immunotherapy; sIgE = specific immunoglobulin E; SPT = skin-prick testing.

criteria for SU challenge decline because they have incorporated the OIT food into their diet and do not want to abstain for a month. Such patients often decrease or eliminate their maintenance OIT dose independent of the supervising clinician. This approach is particularly common among patients who have performed OIT for milk, egg, and wheat.

MANAGING THE PATIENT IN OIT IN SCHOOL

Communication with the school about the patient in OIT is important to make the school aware of the OIT treatment. During the escalation phase of OIT, the school should continue to assume that the child is allergic to the food and adhere to the child's food allergy protocols, including avoidance of the food, and appropriate management of accidental exposures and reactions if they occur. The nature of the communication with the school once escalation is complete will depend on the escalation target. For those patients who have escalated to a bite-proof target, the school should be provided a letter that explains OIT and that, although the reaction risk has been reduced, the patient is continuing to avoid his or her allergenic food and the school's approach to the patient with food allergy should not change. For those patients who have escalated to a free-eating target, once maintenance is reached, further communication with the school is needed to explain that the patient has been treated for the food allergy and should no longer be subject to the restrictions imposed on children with food allergy. The letter should note that, although the risk of a food allergy reaction has been markedly reduced, the risk is not zero and epinephrine should continue to be available in the event of a reaction.

MANAGING THE PATIENT IN OIT AT SUMMER CAMP

Summer camp, particularly sleep-away camp, presents many challenges for patients on daily OIT. Varied daily

schedules, activities that include exercise, decreased sleep, decreased adult supervision, and remote locations at a far distance from hospitals and emergency medical facilities should be considered. The camp medical staff and administration should be fully informed about the patient's food allergies and the status of their OIT treatment. In addition to providing a food allergy action plan, arrangements should be made to provide the OIT food as well as an appropriate predose snack unless there is a plan to dose with a meal. Patients in OIT who have incorporated their OIT food into the routine diet may want to limit the quantity of the OIT food while at camp to decrease the risk of an exercise-triggered reaction.

The most difficult aspect of OIT for the child at summer camp is the post-dose activity limitation. Although OIT dosing at camp, as with many other aspects of OIT, must be individualized, many campers and camp administrations find dosing 1 hour before lights out to be the best time to administer the OIT dose. However, this approach requires that the bunk counselors have a thorough understanding of the need for post-dose activity limitation so that they will prevent rough play during that hour. Because there is a presumption that the risk of a reaction during OIT maintenance is dose related, many practitioners reduce the maintenance OIT dose to 25–75% of the precamp dose for the duration of camp. This can be done whether the patient is in the escalation or maintenance phase of treatment when camp starts. Some families prefer to stop OIT maintenance dosing if overnight camp is $\leq$ 1 week. If OIT dosing is stopped for camp, then the patient should be challenged in the office as soon as possible after camp to determine the appropriate dose to restart OIT. Some summer camps are "nut free." In this situation, the family will have to work with the camp staff to provide nut OIT dosing in the context of the general nut prohibition.

I have tried to present a practical approach to managing patients after the dose escalation target has been reached. These recommendations are based on cited published reports when such reports are available. Recommendations without citations are based on the experience at the Dallas Food Allergy Center and on conversations with other experienced OIT practitioners many of whom have contributed to this issue. Because this issue is intended to be an initial guide to OIT practice, I have not presented an extensive review of the literature. OIT is very much a work in progress and, despite the fact that there are many unanswered questions, the practitioner must make treatment decisions in real time. This article will not be the final answer.

CLINICAL PEARLS

- It is important to clarify the individual OIT goals for each patient so that the maintenance regimen can be customized accordingly.
- Maintenance regimens (dose, dosing frequency, duration) must balance the long-term goals (*e.g.*, free eating or SU) with the patient's ability to adhere to the regimen.
- For many campers in OIT, dosing an hour before lights out is the best way to accommodate the need for postdosing activity restrictions.

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